matter has been added by this amendment. Reconsideration is respectfully requested.

I. Objections to Claims

The Examiner has objected to Claim 27 as including non-elected subject matter. In an earnest effort to facilitate prosecution, claim 27 has been amended to remove the reference to claim 24. Applicants believe that this amendment overcomes the objection to this claim.

The Examiner has objected to claim 25 due to the inclusion of abbreviations in the claims without recitation of the full terminology. As requested by the Examiner, claim 25 has been amended to recite the full terminology of both CPT-11 and APC.

Therefore, Applicants respectfully request withdrawal of the objections to the pending claims.

II. Rejection of Claim 25 under 35 U.S.C. §112, second paragraph

The Examiner has rejected claim 25 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention. Specifically the Examiner suggests that claim 25 is confusing in the recitation of a

"prodrug comprises CPT-11 and APC" as CPT-11 and APC are distinct chemical compounds. In accordance with the Examiner's suggestion, claim 25 has been amended to clarify that the prodrug comprises CPT-11 or APC. Accordingly, withdrawal of this rejection under 35 U.S.C. § 112, second paragraph is respectfully requested.

III. Rejection of Claim 25 under 35 U.S.C. §102(b)

Claims 23, 25, 27 and 28 are rejected under 35 U.S.C. §102(b) as being anticipated by Senter et al. The Examiner suggests that Senter et al. teach methods of increasing the activation of the prodrugs Paclitaxel and camptothecin (CPT-11) to active drugs in human and mouse tumor cells by the administration of rat serum carboxylesterase following administration of the prodrug. Applicants respectfully disagree and traverse this rejection.

Senter et al. teach that a purified enzyme, rat serum carboxylase is responsible for the conversion of paclitaxel-2-ethylcarbonate to paclitaxel. Senter et al. specifically teach that *in vivo* activities obtained from Paclitaxel-2-ethylcarbonate in rodent studies would not reflect the outcome in humans, see column 1, page 1473.

The present invention teaches a method for promoting the cleavage of an ester or carbamate linkage of a prodrug to form an active drug in a cell or organism comprising administering to a cell or organism a prodrug comprising an ester or carbamate linkage and a recombinantly produced carboxylesterase capable of cleaving the ester or carbamate linkage of the prodrug, and forming an active drug in the cell or organism. The recombinantly produced carboxylesterase of the present invention has a leader sequence which is necessary to target the carboxylesterase and for processing through the endoplasmic reticulum.

To anticipate a claim, a reference must teach every element of the claim. See MPEP § 2131. The cited reference does not teach every element of the present invention as claimed.

Senter et al. use a carboxylesterase which has been purified from a naturally occurring mature rat carboxylesterase. It does *not* contain the 18 amino acid leader sequence, which is required for the increased activity found in the recombinant carboxylesterase of the present invention as described on page 25, line 33 through page 26, line 17 and Figure 3. The carboxylesterase of the instant invention is generated by PCR from rabbit liver polyA+ mRNA (page 26, line 19-page 28, line

10). This leader sequence is initially present on the carboxylesterase and is cleaved off during processing through the endoplasmic reticulum and is not present on the mature form of the protein. The naturally occurring carboxylesterase described in Senter et al. does not include the leader sequence which is required for targeting this enzyme to the endoplasmic reticulum and achieving enzymatic activity in the cell. Accordingly, this reference cannot be held to anticipate the present invention.

Withdrawal of this rejection is respectfully requested.

IV. Rejection of Claim 25 under 35 U.S.C. §103

Claim 29 is rejected under 35 U.S.C. §103(a) as being unpatentable over Senter et al. The Examiner admits that Senter et al. do not teach the administration of the rat serum carboxylesterase prior to the administration of the prodrug. However, the Examiner suggests that Senter et al. suggest using the rat serum carboxylesterase for cancer treatment and specifically state that "It may be possible to use rat serum carboxylesterase for prodrug activation *in vivo* by targeting the enzyme to tumors with an appropriate monoclinal antibody and then administering a prodrug such as PC or CPT 11". The Examiner

further suggests that one of skill would be motivated to administer the carboxylesterase first in order for it to be targeted to the tumor prior to prodrug administration as this would minimize side effects due to activation of the prodrug in non-tumor cells. Applicants respectfully disagree.

To establish a *prima facie* case of obviousness under 35 U.S.C. 103(a) three basic criteria must be met. MPEP § 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all of the claim limitations.

The cited reference fails to meet all of these criteria with respect to the instant claimed invention.

Claim 29 depends from claim 23 which has been amended as discussed above to recite that the carboxylesterase is recombinantly produced to include a leader sequence necessary for cleaving of the ester or carbamate linkage of the prodrug and forming an active drug in the cell or organism.

Even assuming arguendo that one of skill in the art would be motivated to administer the carboxylesterase first in order for

it to be targeted to the tumor prior to prodrug administration, the reference would not teach or suggest the leader sequence attached to a prodrug required for cleaving the ester or carbamate linkage of the prodrug and forming an active drug in the cell or organism. Therefore, even if the mature rat carboxylesterase of Senter et al. was recombinantly produced, it would not provide the necessary leader sequence required to increase the enzymatic activity and successfully produce an active drug in the targeted cell or organism. Further, there is no motivation to modify the form of the rat serum carboxylesterase taught by Senter et al., as it is already taught to be effective for its purpose of effecting carbonate hydrolysis of Paclitaxol see column 1, page 1473). There is no suggestion that a leader sequence such as that taught by the present invention would provide any advantage.

Withdrawal of this rejection is respectfully requested.

V. Conclusion

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with Markings to Show Changes Made."

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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Version with Markings to Show Changes Made

In the claims:

Claims 24, 26, 30 and 31 have been canceled.

Claims 23, 25 and 27 have been amended as follows:

23. (Amended) A method for promoting the cleavage of an ester or carbamate linkage of a prodrug to form an active drug in a cell or organism comprising administering to a cell or organism a prodrug comprising an ester or carbamate linkage and a recombinantly produced carboxylesterase capable of cleaving the ester or carbamate linkage of the prodrug, and forming an active drug in the cell or organism.

25. (Amended) The method of claim 23 ~~or 24~~ wherein said prodrug ~~comprises CPT-11 and APC~~ is irinotecan, 7-ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxycamptothecin (CPT-11) or 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino] carbonylcampothecin (APC).

27. (Amended) The method of claim 23 ~~or 24~~ wherein said organism is a human.